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STUDIES ON THE EFFECTS OF GENERAL ANESTHETICS
ON GASTRIC SECRETION

by



E. A. PUIL

A THESIS

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The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies for acceptance, a thesis entitled STUDIES ON THE EFFECTS OF GENERAL ANESTHETICS ON GASTRIC SECRETION submitted by E.A. PUIL in partial fulfillment of the requirements for the degree of Master of Science.



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STUDIES ON THE EFFECTS OF GENERAL ANESTHETICS

ON GASTRIC SECRETION

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ABSTRACT

General anesthesia has been reported to initiate a secretion of high acidity in gastrostomized dogs which exhibit no basal secretion. It was proposed, therefore, that general anesthetic agents produce their secretory effects by some nervous mechanism. The present study was initiated to further analyse the observation that many anesthetics produce gastric secretion in the dog in the absence of surgical trauma.

The cyclohexylamines, CI-395 and CI-581, the derivative of eugenol, FBA.1420, and chloralose-urethane, when given alone in anesthetic doses to gastrostomized dogs, produced gastric acid secretion which appeared to be dependent on the depth of anesthesia. Gastric secretion ceased during emergence from the general anesthetic state.

Atropine given after gastrostomized dogs were anesthetized with chloralose-urethane abolished the secretion evoked by the anesthetic suggesting that the response to anesthesia involved cholinergic mediation. Hexamethonium also completely antagonized this secretion providing evidence that ganglionic transmission is involved in the phenomenon.

Removal of the pyloric antrum in a chronic preparation reduced the acid response to induction of general anesthesia with chloralose-

urethane. The participation of gastrin in the secretory response to anesthesia in intact dogs is, therefore, implicated.

The volatile anesthetics, halothane and methoxyflurane, given by mask or by endotracheal tube did not evoke detectable secretion in doses producing light, surgical and deep anesthesia. In contrast, methoxyflurane administered intravenously in the form of an emulsion, to the same dogs, produced a definite although small acid secretion. It is suggested that the difference between the gastric secretory responses to general anesthetics given by the two routes is due to "opposing" actions by the anesthetic.

The results confirm the observation that general anesthetics given in doses sufficient to produce surgical anesthesia cause gastric secretion by a nervous mechanism.

To
Anne

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I. INTRODUCTION

I. INTRODUCTION

A. GENERAL INTRODUCTION

One of the controversies in the nervous regulation of gastric secretion has resulted from the use of general anesthesia during the experimental procedures. Some studies have avoided the effects of the general anesthetic state by the use of conscious animals with chronically implanted cannulae and electrodes. However, the production of a stable, reproducible condition by a general anesthetic agent is often necessary in many physiological and pharmacological investigations for analysis of the physiological mechanism involved.

The results of studies on the anesthetized animals may be difficult to interpret. Anesthesia alters the balance of excitation and inhibition in the nervous system, and in consequence, seriously disturbs homeostatic conditions. Furthermore, the data to be reviewed in the present section indicate that many loci in the central nervous system are likely to be affected by anesthetics. In view of these considerations, it appears that if neurophysiological control mechanisms of gastric secretion are to be sought, a knowledge of the changes which general anesthetics produce in secretion by the stomach is essential. This investigation is concerned with the measurement of secretory changes caused by anesthetics and other pharmacological agents.

B. HISTORICAL REVIEW

1. Central nervous representation of gastric secretion

The demonstrations of Beaumont (1933) and Wolf and Wolff (1943) clearly established that a relationship exists between psychic factors and gastric secretion in man. A major weakness of these qualitative but classical observations is their failure to provide information about central nervous mechanisms which mediate the alterations in gastric secretion. Pavlov (1927) thought that psychic secretion of gastric juice in dogs depended on the integrity of the cerebral cortex and that removal of the cerebral cortex of both hemispheres would result in the disappearance of all conditioned reflexes. However, investigations since that time have shown quite definitely that certain conditioned reflexes can be established in decorticate dogs and cats (Bard, 1961).

Other approaches to the problem of central neural control of gastric secretion have usually involved either stimulation or ablation of brain loci with subsequent measurement of secretory response. Guerver (1901) found that stimulation of the anterior part of the sigmoid gyrus in dogs produced a copious flow of gastric juice that could be inhibited by sectioning the vagus nerves. Ablation of this cortical area resulted in a pronounced drop of gastric secretory output which returned to normal after seven to eight days (Greker, 1909). Watts and Fulton (1934) observed that after stimulation of the premotor area in monkeys an abnormal amount of secretion was present in the stomach at necropsy. Further evidence for the cortical representation suggested by Pavlov was obtained by Davey, Kaada and Fulton (1950). They stimulated an area of the frontal lobe corresponding to the area stimulated

by Guerver and found it to evoke gastric secretion in dogs and monkeys. In the gastric juice obtained, the content of pepsin and mucus was reported to vary with the intensity of stimulation while hydrochloric acid secretion was dependent on the depth of anesthesia. Klopfer (1954) noted a similar dependence in cats while confirming the results of Davey and his associates on stimulation of a circumscribed area situated on the anterior sigmoid gyrus just anterior to the cruciate sulcus.

Although no other portion of the cerebral cortex was found in the foregoing studies to influence gastric secretion, fronto-temporal regions which are known to effect patterns of emotional behavior markedly influence autonomic control of visceral function. Gastric secretion has been reported to be altered in unanesthetized animals upon stimulation of specified loci on the medial frontal cortex (Sen and Anand, 1957a) and on the post orbital surfaces of the frontal lobe (Anand and Dua, 1955; 1956; Sen and Anand, 1957b). These areas participate in the limbic system which is primarily concerned with the organization of activities of attack, defense, feeding and search for food. Thus Anand and Dua (1955; 1956) observed that marked and varied changes in the affective behavior of cats and monkeys also occurred in parallel with fluctuations in hydrochloric acid secretion upon stimulation of other limbic areas such as the pyriform cortex, hippocampus, temporal tip, anterior cingulate gyrus and amygdaloid regions. Recently, Abiko, Matsuo, Okinaka and Nakao (1966) were able to obtain gastric acid secretion in dogs under morphine anesthesia by stimulating exposed prepyriform cortex. The impulses originating in this post orbital area were believed to be transmitted vagally to the stomach because cutting the vagus nerves inhibited the acid secretion.

There is little evidence regarding the descending pathways mediating the secretory response elicited by stimulation of the fronto-temporal regions. A direct projection of the orbital area to the thalamus has been described since prefrontal lobotomy leads to retrograde degeneration of the large cells of the dorsomedial thalamus (Freeman and Watts, 1947). Sen and Anand (1957a) produced gastric secretion on stimulation of the dorsomedial thalamus of conscious cats and hence considered the possibility that the gastric effect elicited by stimulating the frontal cortex was mediated by the thalamus.

The results of experiments involving neurosurgical procedures do not support the evidence for participation of the projection to the thalamus but rather indicate a functional representation of gastric secretory activity in the cingular cortex and connecting limbic structures. Prefrontal lobotomies, prefrontal lobectomies, unilateral and bilateral cingulate gyrus resections, and insular and pituitary resection in dogs have been demonstrated to lower acid output during an early period. After the stress of surgery passes, however, only bilateral cingulate gyrus resection has been shown to produce a consistent, prolonged diminution of acid secretion (Richter, Davis, Ruge and Walter, 1956). Upon comparing the results of their neurosurgical studies before and after vagotomy, Richter and his co-workers have suggested that the cingulate gyrus exerts its profound effect via a vagal pathway.

In one study, Sen and Anand (1957b) failed to get any change in resting secretion on stimulation of the anterior cingulate gyrus in cats with implanted electrodes. However, both stimulation and inhibition of acid responses in the stomach have been produced by electrical

stimulation of all limbic structures (Anand and Dua, 1955; 1956). Also, Zawoiski (1967a) demonstrated prompt and significant increases in total acid output of conscious cats on stimulation of the corpus callosum-cingulate gyrus area without concomitant behavioral or somatomotor changes. Several descending pathways to the hypothalamus which could mediate the gastric responses elicited by cingulate gyrus stimulation were considered by these investigators but remain conjectural. There appears little doubt, however, that the anterior cingulate gyrus plays an important role in regulating gastric secretory function.

A consistent gastric secretory response can be obtained in unanesthetized, unrestrained cats following stimulation of specific regions in the amygdala. Sheeley and Peele (1957) reported that stimulation of central, lateral and basal components of the amygdala causes a definite increase in gastric acid content which compared favorably with that after histamine administration alone. They suggested that the amygdala effects were mediated through a histaminergic or parasympathetic mechanism. Anand and Dua (1955; 1956) and Sen and Anand (1957b) drew attention to a possible relationship between the basolateral area of the amygdala and the anteromedial hypothalamus in their studies of the limbic system. Since these two areas yielded qualitatively the same acid responses upon stimulation in cats with indwelling electrodes, these investigators concluded that the amygdaloid impulses were conducted through the anteromedial hypothalamus. Gastric acid responses produced by stimulating the lateral amygdala and anterior amygdala-globus pallidus areas have been observed to be similar to responses elicited by supraoptic stimulation. Both responses exhibit relatively short latent periods and similar secretory

patterns at increasing intensities (Zawoiski, 1967b). On the basis that the amygdala sends projection fibers to the preoptic area and antero-medial hypothalamus, the latter investigator supports the view that the amygdala mediates gastric secretory activity through these regions of the hypothalamus.

Some of the earliest observations of hypothalamic influences on visceral function indicated that a parasympathetic center existed within the anteriorly-placed nuclei. The more posterior regions, anatomically under anterior hypothalamic control were believed to serve sympathetic functions. Beattie (1932) showed that stimulation of the tuber cinereum caused profuse acid secretion concomitant with other parasympathetic effects such as increased peristalsis and slowing of the heart. Heslop (1938) found confirmation for these earlier studies since he showed that electrical stimulation of sensitive spots in the tuberal and supraoptic regions generally increased acid secretion. These experiments further demonstrated that the more posterior regions, namely the mammillary nuclei, on stimulation produce a marked increase in mucus content and a tendency to diminish the rate of flow and acidity of gastric juice. Since these effects were accompanied by other manifestations of a sympathetic nature elsewhere in the body, Sheehan (1940) in his review of hypothalamic stimulation experiments maintained that sufficient evidence existed for accepting a sympathetic center regulating gastrointestinal activity. Although the precise anatomical localization of the center was not given, the posterior hypothalamus was noted as being particularly responsive.

The results of investigations by Kosenko (1958) show that stimulation of the posterior hypothalamus does give a sympathetic response. For example, stimulation of the hypothalamus at the level of the posterior border of the hypophysial infundibulum in conscious dogs produces a small increase in mucus secretion without rise of acidity or of pepsin content. Conversely, a secretion of large amounts of gastric juice with high acidity was obtained on stimulation of the anterior part of the hypothalamus. This latter effect has always been interpreted as parasympathetic in nature.

The existence of functionally specific autonomic regions in the brain has met with criticism. It is well known, for example, that both sympathetic and parasympathetic effects can be obtained by stimulation of the same point (Gellhorn, 1957). Indeed, the fact that Beattie used a Harvard inductorium to stimulate the tuber cinereum raises the additional question of the border areas activated by the uncalibrated current. On the other hand, activation of very closely situated points may have entirely different effects on various autonomic mechanisms (Kaada, 1960). Thus Anand and Dua (1956) conclude that different points within the same anatomical brain structure produce excitation and inhibition of autonomic mechanisms effecting gastric secretion.

Nevertheless, the mechanism whereby hypothalamic stimulation produces alterations in gastric secretion does require an explanation and while most investigators agree that the gastric effects are mediated by the vagus nerves, others maintain that an extravagal mechanism is also involved. Whereas Beattie (1932) observed that sectioning the vagus nerves abolished both the gastric and cardiac effects, anterior

hypothalamic stimulation in cats with complete transthoracic vagotomy was reported by Heslop (1938) to be successful in accelerating the flow of gastric juice as well as raising the acidity.

Support for the implied extravagal influence was gained by Porter, Movius and French (1953a) who induced hydrochloric acid secretion by stimulating the anterior or posterior regions of the hypothalamus of rhesus monkeys anesthetized with chloralose and cyclopropane. Upon comparing the considerable latency (one to two hours) of change in acidity evoked by posterior hypothalamic stimulation to the rapid onset of acid secretion following anterior hypothalamic stimulation, they repeated the experiments in vagotomized monkeys and found only the response obtained by stimulation of the anterior nuclei to be abolished. Adrenalectomy, however, blocked the delayed response obtained by stimulation of the posterior region. These authors have advanced a hypothesis of dual hypothalamic pathways controlling acid secretion by the stomach; the first originates in the anterior hypothalamus and reaches the stomach by way of the vagus nerves, the second pathway emanates from the posterior hypothalamus and is mediated by the pituitary-adrenal system.

With the exception of the original observations of Porter and his associates (cf. Porter et al., 1953a) on which the hypothesis is based, the evidence in favor of a dual mechanism is relatively scanty and only indirect. Gastric acid secretion has been reported to increase after posterior hypothalamic stimulation in chloralosed cats (Feldman, Birnbaum and Behar, 1961) and in conscious dogs with implanted electrodes (Kosenko, 1957; Feldman and Birnbaum, 1965; Mason and Nelsen, 1967).

The anterior hypothalamus and dorsal hippocampus have been observed to modify the effects of the posterior hypothalamus on gastric secretion. Thus electrical stimulation of the posterior hypothalamus together with stimulation of either the anterior region or the dorsal hippocampus results in a marked diminution of gastric secretory activity (Feldman, Wajsbort and Birnbaum, 1967). In these studies, however, the responses obtained following stimulation of anatomically similar areas within the hypothalamus in different cats were not uniform and the authors emphasize that no consistent correlation appears to exist between the secretory response and the anatomical area stimulated.

Nevertheless, the hypothalamus seems to possess inhibitory components which may be influenced by other neural areas. This might explain why stimulation of the posterior hypothalamus failed to alter basal secretion in some studies (Sen and Anand, 1957c); Kosenko, 1958; Leonard, Long, Thomas, Nicoloff and Wangensteen, 1963; Leonard, Long French, Peter and Wangensteen, 1964a) while it blocked histamine-induced secretion in others (Leonard et al., 1963; 1964a; Leonard, Engle, Peter, Long and Wangensteen, 1964b) and in others it produced a delayed acid response mediated via the pituitary-adrenal axis (French, Longmire, Porter and Movius, 1953a; Porter et al., 1953a; Porter, Longmire and French, 1953b).

Although some support for extravagal influences was obtained from other experiments in which hydrochloric acid secretion was induced with stress stimuli (French et al., 1953a), Smith and Brooks (1967) point out that the original experiments of Porter and his co-workers remain the sole physiological evidence for an "adrenal phase"

of gastric secretion activated by hypothalamic mechanisms. The experiments of Kosenko (1968) indicate some humoral participation since he found acid secretion in chronically vagotomized dogs with divided splanchnic nerves to be abolished only by bilateral adrenalectomy.

Some data obtained from studies on unanesthetized dogs are not in accordance with this hypothesis since either anterior or posterior hypothalamic stimulation produces a marked rise in plasma adrenocortical hormones but no increase in hydrochloric acid secretion (Zukoski, Lee and Hume, 1963). Similar studies in conscious macaque monkeys also failed to reveal increases of acid secretion despite elevated plasma corticoids after hypothalamic stimulation (Smith and McHugh, 1964). In addition, adrenocorticotrophic hormone has been reported to have no effect on gastric secretion (Dragstedt, Ragins, Dragstedt and Evans, 1956; Ragins, Dragstedt, Landor, Lyon and Dragstedt, 1956). The apparent dissociation, therefore, of plasma levels of adrenocortical hormones and the gastric effect may limit the significance of the hypothalamic-pituitary axis in neural control of gastric secretion.

Other investigators have demonstrated the occurrence of an acid secretion of rapid onset following electrical stimulation of the anterior hypothalamus both in anesthetized (Porter et al., 1953a; 1953b) and in conscious (Sen and Anand, 1957c; Kosenko, 1957; 1958; Leonard et al., 1963) animals. The absence of a secretory response following anterior or posterior hypothalamic stimulation has been attributed by Leonard et al., (1963) to the type of stimulating current.

They observed that high frequency (200 cycles/second) stimulation of the anterior region of the hypothalamus was much less effective in evoking gastric secretion than low frequency (5 cycles/second) stimuli. Posterior hypothalamic stimulation either at high or low frequencies not only failed to cause secretion but markedly reduced the secretion induced by histamine. These findings suggest that a high frequency type of stimulus may activate nearby sympathetic centers or release inhibitory factors which act to prevent acid secretion. The activation of inhibitory pathways may provide some reason for the variable onset of secretory response observed after posterior hypothalamic stimulation and may be applied as criticism to the "dual hypothesis".

None of the electrophysiological studies previously mentioned, save for that of Mason and Nelsen, have considered the creation of lesions from unidirectional stimuli as a possible reason for the disparity of results. Mason and Nelsen (1967) found, for example, that stimulation of the anterior, middle or posterior hypothalamic regions in conscious dogs with symmetrical biphasic square waves of low frequency (10 cycles/second) produced a consistent increase in acid secretion with the same temporal relations in each case. That lesions and stimulation cause opposite effects in the same hypothalamic areas has been known for a number of years (Sheehan, 1940). Similarly, the necrosis and scarring of tissue that follows prolonged monophasic stimulation of the brain (Rowland, MacIntyre and Bidder, 1960) may provide another reason for the variation of results of the chronic studies.

The deliberate use of electrolytic lesions, on the other hand, has provided the first evidence for a recently proposed mechanism of alimentary control in the rat. Ridley and Brooks (1965) found that placement of lesions in a discrete portion of the medial hypothalamus of gastric fistula rats resulted in hyperphagia and a pronounced hypersecretion of acid in the resting state. Electrical stimulation of the area inhibited food intake and inhibited insulin-induced gastric secretion (Misher and Brooks, 1966). In contrast, stimulation of the lateral region produced an increase in food intake and increased gastric secretion; effects which could be abolished by bilateral vagotomy. Smith and Brooks (1967) suggest that the critical areas for controlling food intake and gastric secretion coincide i.e., lesions or stimulation of areas which do not alter food intake have no effect on gastric secretion. Their conclusion is that the medial region inhibits the lateral hypothalamus during satiety, but during feeding, the lateral region becomes dominant because of release from inhibitory influences emanating from the medial region. Gastric secretion is caused when impulses originating in the lateral hypothalamus are conveyed through the vagus nerve to the stomach.

The hypothesis that neural regions involved in alimentary control are correlative with feeding behavior is attractive since feeding may be considered a natural stimulus for gastric secretion. The observation that stimulation through chronic electrodes implanted in the lateral hypothalamus of conscious monkeys produced "defense reactions" and marked inhibition of gastric acid output (Smith and McHugh, 1964) does not correspond with the effect obtained upon

stimulating the lateral region in the rat, but is consistent with the suggested integrative action of the hypothalamus in behavior and gastric secretion. On the other hand, this hypothesis has the limitation of not being applicable to all species since the level of neurological development of the rat may not be representative of other species. Zawoiski (1967a), for example, found no significant gastric secretory response on stimulation of the lateral hypothalamus of cats even at intensities which produced overt behavioral changes. Another limitation is that although a structural basis for autonomic control of gastric secretion related to behavior is presented for the rat, it does not explain the lack of hypersecretion in mice made obese with gold thioglucose (Brooks, 1966). Gold thioglucose administration to mice produces lesions restricted to the ventromedial hypothalamus (Mayer and Marshall, 1956). Thus if this "satiety" area were to be destroyed by this agent a profuse acid secretion in the stomach would be expected to accompany the observed hyperphagia.

The evidence used in support of above hypothesis that electrical stimulation of the medial hypothalamus inhibited insulin-induced gastric secretion might indicate the involvement of other structures besides the hypothalamus. Jögi, Ström, and Uvnäs, (1949) have evidence that vagal medullary centers are also sensitive to insulin-induced hypoglycemia, the stimulus used by Brooks and his associates. Similarly, no cognizance is taken of the possibility that the cerebral cortex may be intimately involved in the proposed control mechanism. A role for the frontal cortex is likely since this area in dogs inhibits the exciting influences of the hypothalamus on the function of the alimentary glands (Bogach, Kosenko and Nesen, 1962). The activation of

non-neurogenic inhibitory factors, such as changes in blood flow to the stomach which act to prevent acid secretion, must also be considered.

The greatest weakness of the behavioral hypothesis at present is the lack of knowledge of the neuroanatomical organization of pathways within the hypothalamus of different species to either substantiate or disprove its postulates. Evidence gained from the experiments of Brooks and his co-workers (cf. Smith and Brooks, 1967) is at best equivocal since more than one interpretation is possible. In addition to the similarities that this hypothesis shares with the concept of a rostral parasympathetic mechanism balanced against that of a more caudal sympathetic one, it also bears resemblance to the "dual hypothesis" and in some respects shares its disadvantages.

Thus far, no single theory can account for the control mechanism of gastric secretion on a neuroanatomical, neuroendocrinal, or behavioral basis. The importance of the hypothalamus and the limbic system as a central integrating unit for the regulation of gastric secretory activity, however, has been well established. The existence of other neural aggregates contributing to a control mechanism is also likely. Hockman, Papadopoulos and Hoff (1963), for example, have reported changes in gastric secretion on electrical stimulation of points in the "central grey" matter of anesthetized cats. Zawoiski (1967a) found no significant secretory response on stimulation of sites located in the reticular mesencephalic substance of conscious cats but Bakuradze (1962) was able to establish that in dogs the reticular formation exerts a stimulating influence on the secretory activity of the stomach by activating vagal centers. Pradhan, Gupta and Sen (1966) were also able

to demonstrate increases in gastric acid output in conscious dogs on stimulation of several parts of the reticular formation, especially in the medullary region. That the reticular formation is an important integrating center for the control of many autonomic functions is well known but whether the gastric effects are controlled by the reticular formation or the hypothalamus, or both, is not clear. Eliasson (1960) points out that if a change takes place in one part of the brain as a result of emotion, it will be reflected in the reticular formation. Since the reticular formation can feed impulses to the hypothalamus, the reticular depression which is caused by anesthetics and other general depressant drugs (French, Verzeano and Magoun, 1953b), may free the hypothalamus from controlling influences from reticular structures and be reflected in autonomic activity such as gastric secretion.

2. General depressant drugs and gastric secretion

For nearly a century, general depressant drugs have been employed as general anesthetics in most acute studies on gastric secretion. The effects of these agents per se on the secretory function of the stomach have not been closely examined. Merendino (1948a), however, has reviewed and investigated the stimulating influence of morphine on acid secretion in dogs with various pouches. But the use of morphine to produce deep narcosis or anesthesia-like conditions for gastric secretion experiments has been rare. In addition, morphine, like ether, possesses a strong hyperglycemic action which contraindicates the use of either agent in experiments in which gastric secretion is induced by insulin administration (Jögi and Uvnäs, 1949).

While there may be some doubt about the exact mechanism by which insulin administration causes gastric secretion, the prompt inhibition of this response by inhalation anesthetics such as halothane, was considered by Barrett, Raventos and Siddall (1966) to be due to a block of vagal impulses from reaching the stomach. These workers observed that in rats under 1% halothane anesthesia, insulin was devoid of any secretory action. Also halothane, and to a lesser degree ether, only reduced the secretory response induced by a pentagastrin, I.C.I. 50,123. Earlier, Raventos (1961) demonstrated that the administration of 0.75% halothane to cats completely abolished the acid secretion produced by electrical stimulation of the peripheral ends of the severed vagi. Taking into consideration other observed actions of halothane on the autonomic nervous system, Raventos concluded that the observed inhibition was not due to a direct action on the parietal cells but rather to an action on

the postganglionic neurons of the stomach. The ganglionic blocking properties of halothane and other inhalation anesthetics have been described (Garfield, Alper, Gillis and Flacke, 1968) but whether this action underlies the depressant effect of ether or ethylene on gastric secretion in man (Johnston and Ivy, 1926) has not been studied.

In addition to producing depressant effects, inhalation of ether (also nitrous oxide or cyclopropane) can also elicit excitatory responses both centrally, and peripherally, which have been attributed to the depth of anesthesia (Rossi and Zirondoli, 1955). The relatively constant depth of anesthesia produced by the intravenous administration of a barbiturate has long been considered a desirable condition favoring the use of barbiturates in experiments pertaining to gastric secretion.

Tatum and Parsons (1922) first aroused interest in this regard when they stated that gastric secretion in dogs under barbital anesthesia was "far superior" to that observed under ether anesthesia. In the reports that followed, several of the barbituric acid derivatives were demonstrated to have inhibitory effects on stomach secretions. Anesthetic doses of barbital have been shown to depress insulin-induced gastric secretion in dogs (LaBarre and Wauters, 1932) and acid secretion evoked by an intravenous injection of a pentagastrin in rats (Barrett et al., 1966). Olmsted and Garagossintz (1930) described some effects of amobarbital anesthesia in dogs on gastric acidity and volume using the alcohol test meal and aspirations. They concluded that amobarbital prevented gastric secretion. Amobarbital anesthesia has been reported to depress pilocarpine-induced gastric secretion in a dog with a

denervated pouch (Montgomery, 1935) while barbital or amobarbital administered intravenously produced a reduction of gastric secretory volume in Pavlov and Heidenhain pouch dogs which were fed prior to the induction of anesthesia with these agents (Coffey, Koppanyi and Linegar, 1940). Gastric acid secretion in dogs has been shown to be reduced by pentobarbital anesthesia whether the secretion was basal or spontaneous in origin (Jaffe and Friedman, 1959; Laureta and Texter, 1965), induced by insulin (Jögi and Uvnäs, 1949; Powell and Hirschowitz, 1967) or by histamine administration (Marks, Komarov and Shay, 1958; Skyring, Milton and Maxwell, 1961; Powell and Hirschowitz, 1967).

Woo and Brooks (1963) reported anomalous results which suggested that the depressant effect of barbiturates on gastric secretion might be largely dose-dependent. Sodium pentobarbital given intraperitoneally to spider monkeys in subanesthetic doses (15 mg per kilogram of body weight) did not change the volume or acid output of secretion from control values. Jaffe and Friedman (1959) tested thiopental and pentobarbital over a wide range of subanesthetic doses in dogs. They found only a reduction or cessation of spontaneous secretion or secretion induced by a food stimulus, in fistulas or Pavlov pouches. In both Pavlov and Heidenhain pouch dogs, acid secretion induced by 0.5 mg of histamine acid phosphate was found to be markedly reduced by sedative doses of phenobarbital or its sodium salt although no depressant effect on gastric secretion following sedative doses of sodium phenobarbital was evident in man (Merendino, 1948b). Sedative doses of sodium phenobarbital were also found to reduce insulin-induced gastric secretion in dogs while hexobarbital anesthesia prevented secretion from occurring

despite pronounced hypoglycemia (Varro and Olah, 1954). The rectal administration of hypnotic doses of amobarbital or chloral hydrate caused a considerable fall in the amount of hydrochloric acid secreted by Heidenhain pouch dogs fed a test meal (Amirov, 1957).

The inhibition or absence of secretory activity following administration of a barbiturate is not invariably the case. Jögi and Uvnäs (1949) found, for example, that the secretory response to histamine in the dog was not significantly depressed by anesthetic doses of sodium pentobarbital. About the same time, Ballem, Noble and Webster (1948) demonstrated that ethyl 3:3 dimethylallyl barbituric acid (16-A) causes the secretion of a highly acidic gastric juice in the dog. The stimulant action of this barbiturate and another derivative, ethyl 1:3 dimethyl-1-butenyl barbituric acid had been noted earlier in the cat (Noble, 1945). Noble and his co-workers concluded that the observed effect was the result of a central action since the secretory response caused by 16-A was prevented by supra-diaphragmatic vagotomy, sodium pentobarbital anesthesia, or tetraethylammonium, a ganglionic blocking agent. The secretion of a highly variable volume of gastric juice in dogs anesthetized with sodium thiopental or sodium pentobarbital has been reported by Schachter (1949). Although an absence of secretion was observed in one experiment with pentobarbital anesthesia, a small, erratic but significant secretion of high acidity occurred approximately two hours after induction of anesthesia with thiopental or pentobarbital.

Schachter (1949) also investigated the secretory response of dogs anesthetized with other general anesthetics. He found that

anesthesia with chloralose, urethane or chloralose-urethane caused a marked secretion of very acidic gastric juice which could be prevented by atropine, surgical trauma, or acute vagal section. Chronic cervical vagotomy did not prevent the secretion of slightly acidic gastric juice in a dog anesthetized four weeks post-operatively with chloralose-urethane and precluded any conclusions that the phenomenon was entirely of central nervous system origin. The secretory response of dogs anesthetized with chloralose has been noted by Jögi and Uvnäs (1949) and Laureta and Texter (1965) although Jaffe and Friedman (1959) were unable to detect any secretory response to a wide range of doses of chloralose or chloralose-urethane. Urethane administered to rats by a number of different routes has been reported to reduce secretion which was basal (Komarov and Bralow, 1960), induced by insulin (Bralow, Komarov and Shay, 1961), induced by gastrin or a pentagastrin (Barrett et al., 1966).

Thus a number of conflicting reports concerning the effects of general depressant drugs on gastric secretion exist. The majority of authors reviewed, agree that general anesthetics have an inhibitory effect on gastric secretion irrespective of the basal condition of the fundic cells or the secretory stimulant employed. The studies of Schachter (1949), however, have shown that this may not necessarily be the case and this matter appears to require some resolution.

C. STATEMENT OF THE PROBLEM

The aim of this work is to investigate the possibility that general anesthetics exert a stimulatory effect on gastric secretion. If this be the case then some explanation for the seemingly different reports in the literature (see B-2, Introduction) regarding the effect of anesthetic agents must be advanced. Most clinically used general anesthetics produce a stage of excitement (Stage II anesthesia) which is held due to suppression of the activity or effects of inhibitory neurones in the central nervous system (French et al., 1953b). On the other hand, general anesthetics are capable of producing a more direct action on autonomic effector cells e.g., halothane and cyclopropane are known to potentiate responses to postganglionic stimulation (Garfield et al., 1968). Thus the stimulatory effect of general anesthesia on gastric secretion (cf. Schachter, 1949) may be the result of either disinhibition of central nervous activities which influence gastric secretory function or a postganglionic action on local nervous reflexes within the stomach walls controlling its glandular secretion.

The experiments reported here were designed to study:

- 1) the gastric secretory response after induction of anesthesia in the intact animal.
- 2) to analyse, as far as possible, the mechanism whereby anesthetic agents affect gastric secretion observed in 1).

II. EXPERIMENTAL

A. METHODS

1. General methods

All experiments in this investigation were performed on adult mongrel dogs of both sexes weighing from 12 to 24 kilograms. The experimental procedure involved anesthetizing a dog which had undergone a gastrostomy at least three weeks prior to the administration of an anesthetic and subsequently measuring gastric secretion. Between successive experiments on the same dog, the animal was allowed to recover for a minimum of three weeks before being re-anesthetized.

All dogs were fed a standard diet of meal and meat, and to reduce psychic secretion just prior to anesthesia, the animal was never fed in the laboratory nor by the experimenter. Presence of chyme after a 30 hour fasting period was rare and if encountered, the experiment was terminated. At the end of the fasting period i.e., just before induction of anesthesia, the pH of the stomach was checked with indicator paper. Only those dogs exhibiting a neutral or alkaline pH, with no basal secretion detectable, were administered anesthetic. Immediately following the induction of anesthesia, the animal was suspended in a cloth frame with the head of the animal lowered to insure external drainage of any saliva. A collection device was attached to the stainless steel or brass cannula and juice collected from the fistula.

2. Surgical preparation

General anesthesia was induced with intravenous thiopental sodium (25 mg/kg) and following intubation, was maintained with halothane or methoxyflurane vapor.

All surgery was performed using sterile technique. With the animal in the supine position and the abdomen prepared appropriately with shaving, soap-wash, and disinfectant, a 15 cm midline laparotomy was performed. The stomach was easily delivered into the wound. The left gastric and gastroepiploic arterial supply to the stomach was temporarily interrupted with a long gastrointestinal clamp placed transversely across the cardia during the operation. In an area of the main body of the stomach visibly free from blood vessels, a 3 cm longitudinal incision was made and a cannula inserted and secured with a 0 silk pursestring suture. A drawing depicting the relative position of the cannula in the stomach is shown in Fig. 1(A). Following cleansing of the abdomen and inspection of the operative field, the wound was closed using individual layer closures of continuous 2-0 chromic gut. The cannula was brought through the wound cutaneously, secured by continuous running 2-0 silk sutures on the free edges, and plugged with a rubber stopper.

Anesthesia was discontinued and the post-operative course of the animal followed, allowing the dog to feed on liquids for 48 hours before resuming the regular diet.

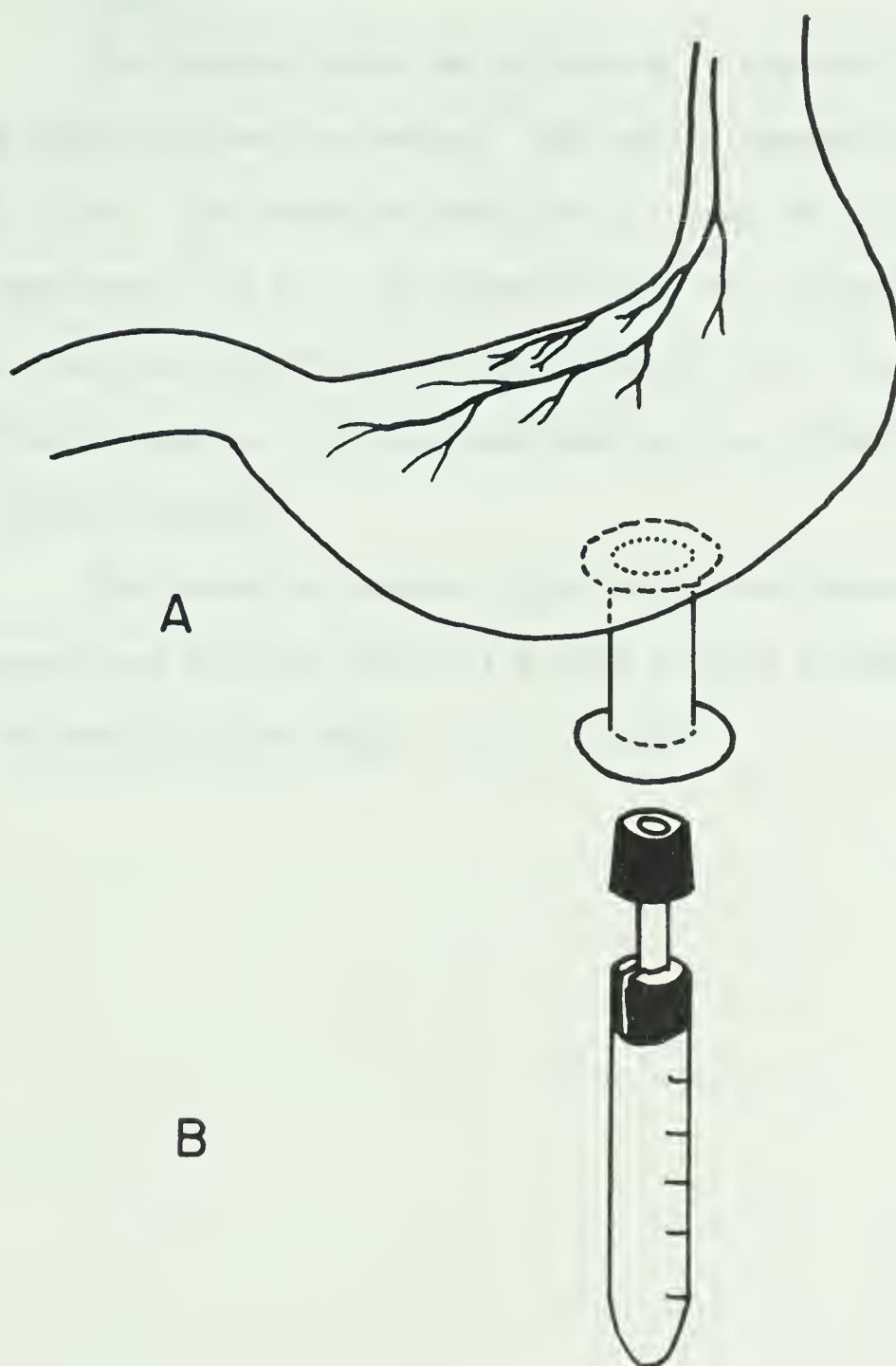


Fig. 1. (A) Diagram showing positioning of cannula in dog's stomach in gastrostomy operation.

(B) Collection assembly attached during anesthesia to cannula shown in (A).

3. Techniques employed for the collection and analysis of gastric juice

The gastric juice was collected in a measuring cylinder attached to a rubber collection device. The entire assembly is illustrated in Fig. 1 (B). The measuring tube had a volume of 15 ml and was graduated in one-tenth of a ml. The gastric juice was allowed to drop continuously down into the cylinder where the secretory rate could be determined at desired intervals. In most experiments, the cylinder was emptied at 20 minute intervals.

The volume of gastric juice collected during an interval was measured and titrated with 0.1 N NaOH or 0.05 N NaOH using phenolphthalein as an indicator (pH range - 8.2 to 10.0).

B. EFFECTS OF INTRAVENOUS ANESTHETICS ON GASTRIC SECRETION

1. General methods.

General anesthetics were injected into either the ante-brachial cephalic or external saphenous vein of a shaved leg. Induction of the unconscious state was smooth, in most cases, with no apparent pain at the injection site. Upon transferring the unconscious animal to the cloth frame, gastric secretion was measured at 20 minute intervals and the course of anesthesia was noted. The conjunctival response to touching the corner of an eye and the presence of spinal reflexes e.g., the withdrawal response to pinching of the foot, were criteria used for the depth of anesthesia which was noted throughout each experiment. The conjunctival reflex was not used as a criterion of depth of cyclohexylamine anesthesia. Dogs which exhibited rhythmic respiration but no conjunctival or spinal reflexes were considered to be in a state of 'general anesthesia of surgical depth'. Absence of the above reflexes with additional depression of respiratory rate was regarded as 'deep anesthesia'.

The drugs used were the cyclohexamines, CI-395 and CI-581 (Parke Davis), FBA.1420 (Bayer), alpha-chloralose (Nutritional Biochemicals) and ethyl urethane (Fisher). CI-395 and CI-581 were dissolved in 0.9% saline in amounts which would allow the total volume to be injected to be less than 10 ml. FBA.1420 was injected in volumes not exceeding 10 ml. A 1:10 ratio (by weight) of chloralose and urethane was made by dissolving 2.0 gm of alpha-chloralose with 70 ml of saline heated to 70°. 2.0 gm of ethyl urethane was added to the hot solution with saline to make 100 ml. Upon cooling to 40°, 2.5 ml of this solution per kilogram of body weight

was injected intravenously as an anesthetizing dose. In one instance, a 1:5 solution of chloralose-urethane was made up using the above method and the animal was anesthetized with 3.0 ml of the solution per kilogram of body weight.

2. Results

The purpose of the experiments in this section was to determine if anesthetic doses of general depressant drugs could initiate an acid secretion in animals which exhibit no basal secretion.

a) Responses to CI-395 anesthesia

Following a rapid induction to surgical anesthesia, a highly acidic secretion with a short latency of onset was observed in two dogs anesthetized with CI-395. The results are given in Table I. Both dogs salivated a mucoid type of saliva profusely throughout the duration of anesthesia which was about 85 minutes in both cases. Clonic convulsions and rapid eye movements occurred intermittently in one dog (Magendie) during the first 30 minutes of anesthesia. As the depth of anesthesia became lighter, the secretion diminished. The time course of secretion and acidity during anesthesia is shown in Fig. 2.

b) Responses to CI-581 anesthesia

Like its cogener, CI-395, CI-581 produced a rapid induction to a surgical anesthesia though somewhat deeper. A secretion of short latency of onset was observed and in dog Luschka, secretion appeared almost at the same time as induction. The results have been tabulated in Table II. Slight mucoid salivation was evident during anesthesia. The time course of secretion and acidity during the course of anesthesia are shown in Fig. 3. Both the rate of secretion and acid content decrease with lighter depth of anesthesia.

TABLE I

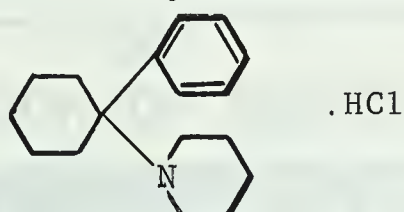
Gastric secretory responses of dogs anesthetized with CI-395*

Collection Time (min after secretion started)	Dog 'Karl'		Dog 'Magendie'	
	Volume** of Gastric Juice (ml)	Acidity (meq/l of HCl)	Volume** of Gastric Juice (ml)	Acidity (meq/l of HCl)
0 - 20	15.2	110.5	12.0	83.3
20 - 40	17.6	101.1	23.1	113.4
40 - 60	20.1	109.4	9.2	123.8
60 - 80	5.1	111.7	2.2	127.7
80 -100	0.0	--	0.1	--

* dose - 3.0 mg/kg

synonyms are: Sernyl^R, Sernylan^R, and Phencyclidine.

chemical structure is: 1-(1-Phenylcyclohexyl) piperidine hydrochloride



** each sample taken represents preceding 20 minute period.

-- indicates sample not analysed.

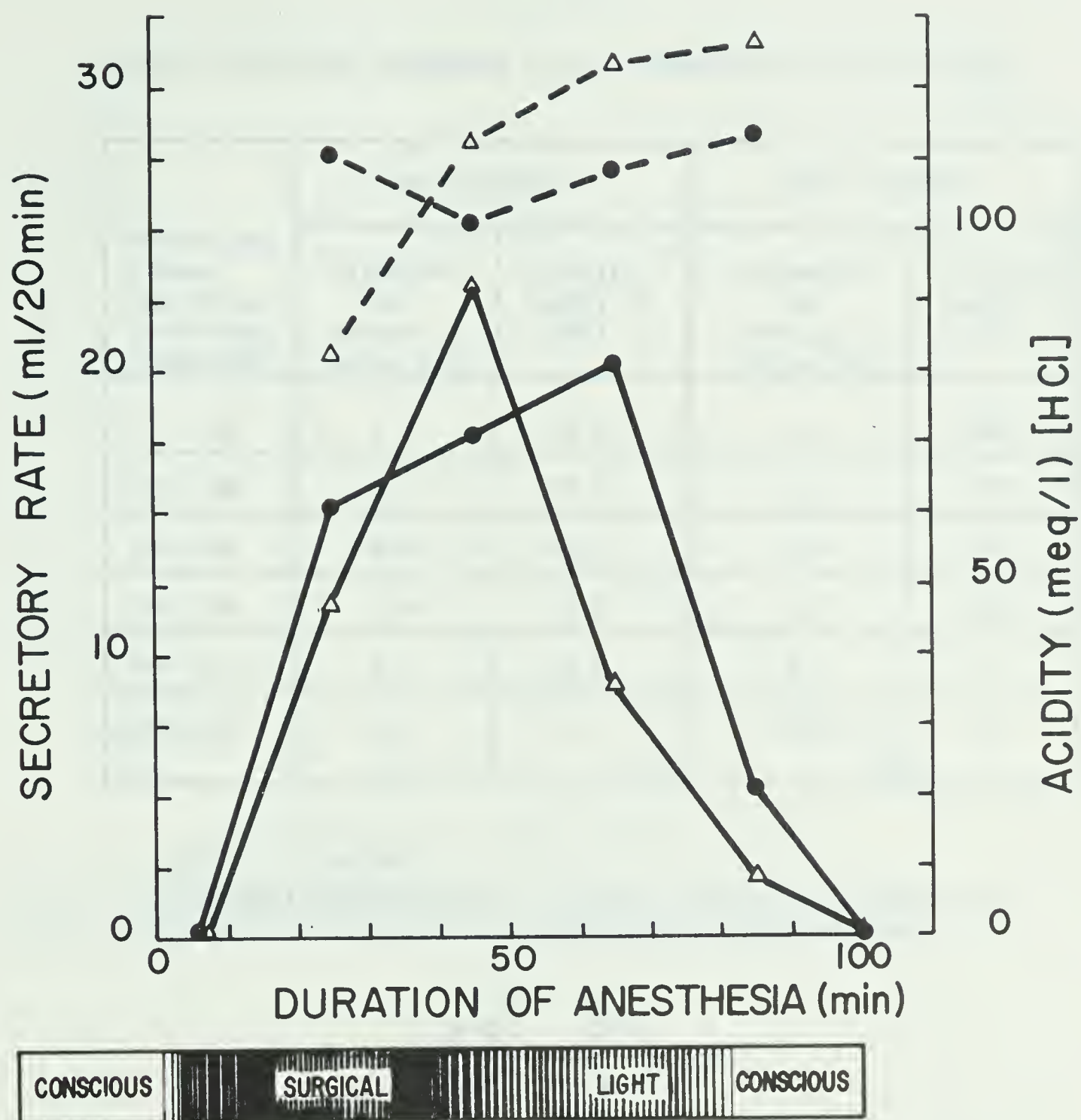


Fig. 2. Time course of gastric secretion during CI-395 anesthesia. ●, dog Karl; △, dog Magendie. Secretory Rate, Solid Line; Acidity, Broken Line.

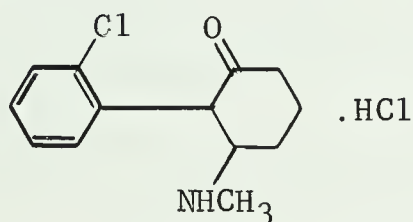
TABLE II

Gastric secretory responses of dogs anesthetized with CI-581*

Collection Time (min after secretion started)	Dog 'Claudia'		Dog 'Luschka'	
	Volume** of Gastric Juice (ml)	Acidity (meq/l of HCl)	Volume** of Gastric Juice (ml)	Acidity (meq/l of HCl)
0 - 20	6.5	78.4	3.4	88.2
20 - 40	2.6	77.0	3.2	87.5
40 - 60	0.8	87.5	3.0	83.3
60 - 80	0.8	25.0	2.0	75.0
80 - 100	0.6	16.6	0.2	--
100 - 120	0.1	--	0.0	--

* dose - 70 mg/kg

chemical structure is: 2-(o-Chlorophenyl)-2-methylamino-cyclohexanone hydrochloride



** each sample taken represents preceding 20 minute period.

-- indicates sample not analysed.

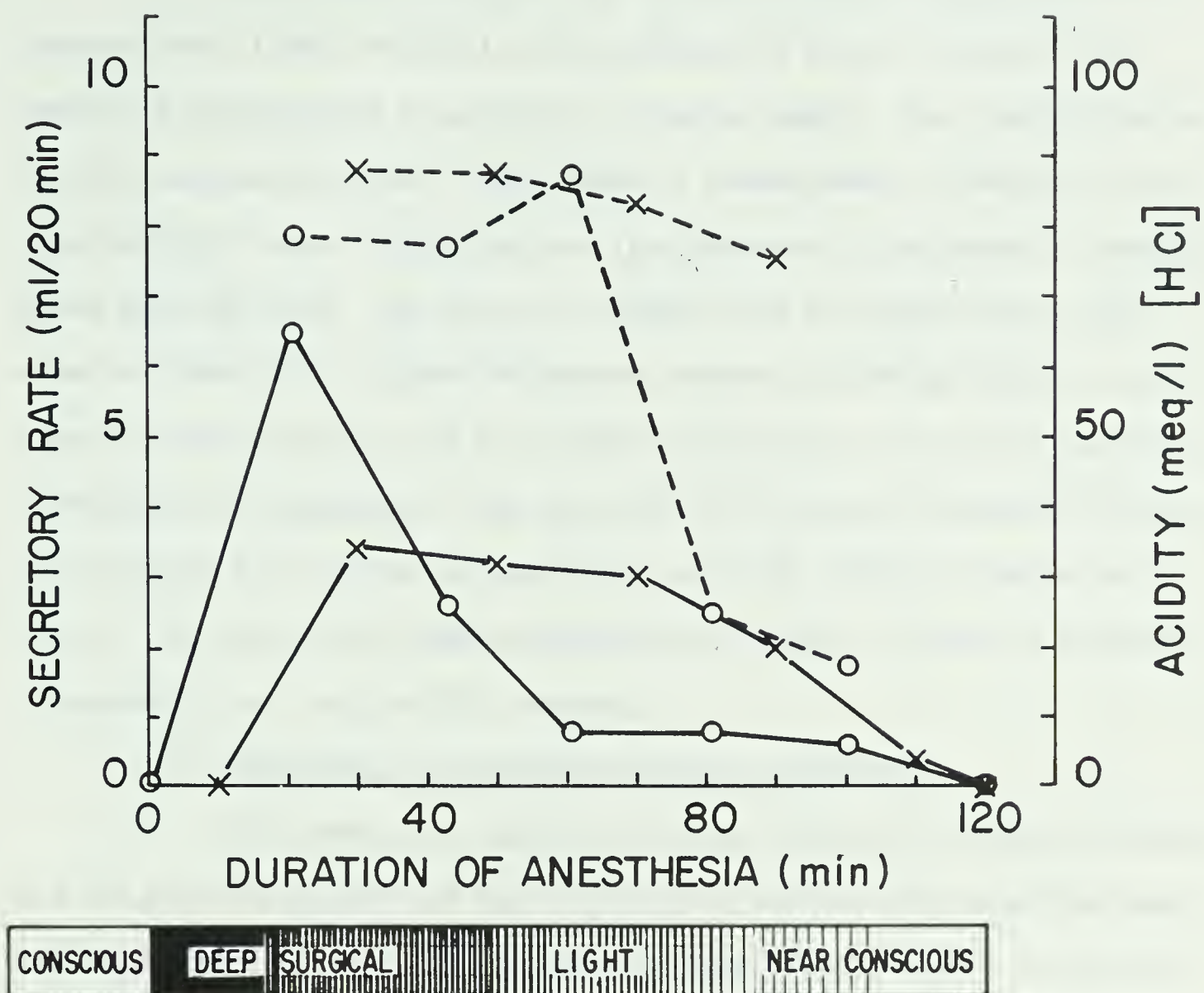


Fig. 3. Time course of gastric secretion during CI-581 anesthesia. ○, dog Claudia; x, dog Luschka. Secretory Rate, Solid Line; Acidity, Broken Line.

c) Responses to FBA.1420 anesthesia.

The initial dose of this extremely-short acting anesthetic produced only light anesthesia and supplemental doses totaling 2.0 gm had to be administered to maintain a surgical depth. Upon administration of the supplemental doses to dog Heinz, a commencement of gastric secretion was soon noted. Secretion was also observed in dog Daniel L anesthetized with FBA.1420. The results obtained from both experiments are shown in Table III. Slight salivation occurred following induction while clonic convulsions with a 2 or 3 minute periodicity occurred in dog Heinz throughout the experiment. The time course of gastric secretion relative to the depth and duration of anesthesia with FBA.1420 is illustrated in Fig. 4. As the animal became progressively lighter in depth, a decrease of secretory rate and acidity occurred.

d) Responses to chloralose-urethane anesthesia.

The onset of secretion following chloralose-urethane anesthesia was relatively slow (30 min in dog Louis and 45 min in dog Penelope). The volume of secretion and its analysis have been tabulated in Table IV. As illustrated in Fig. 5, the degree of acidity appears to parallel the rate of gastric secretion during anesthesia. Secretion appeared to be greatest during surgical anesthesia and declined thereafter with lighter depth.

TABLE III

Gastric secretory responses of dogs to FBA.1420* anesthesia.

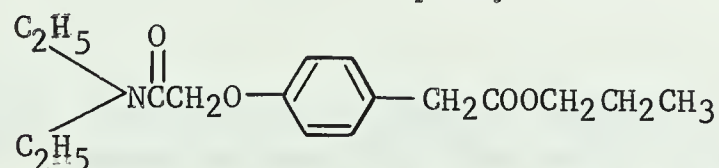
Collection Time (min after secretion started)	Dog 'Daniel L'		Dog 'Heinz'	
	Volume** of Gastric Juice (ml)	Acidity (meq/l of HCl)	Volume** of Gastric Juice (ml)	Acidity (meq/l of HCl)
0 - 20	8.9	89.8	5.5	81.8
20 - 40	16.4	95.7	7.2	122.2
40 - 60			20.5	117.0
60 - 80	0.0	--	9.8	120.4
80 - 100	0.0	--	3.5	160.0
100 - 120			3.5	108.6
120 - 140			2.5	60.0
160			0.0	--

* dose - Daniel L: initially 50 mg/kg
supplementally 0.88 gm

Heinz: initially 60 mg/kg
supplementally 4.5 gm

synonym is Propanidid^R

chemical structure is: 3-methoxy-4-(N-diethylcarbamidomethoxy)
phenylacetic acid-n-propyl ester



** each sample taken represents preceding 20 minute period.

-- indicates sample not analysed.

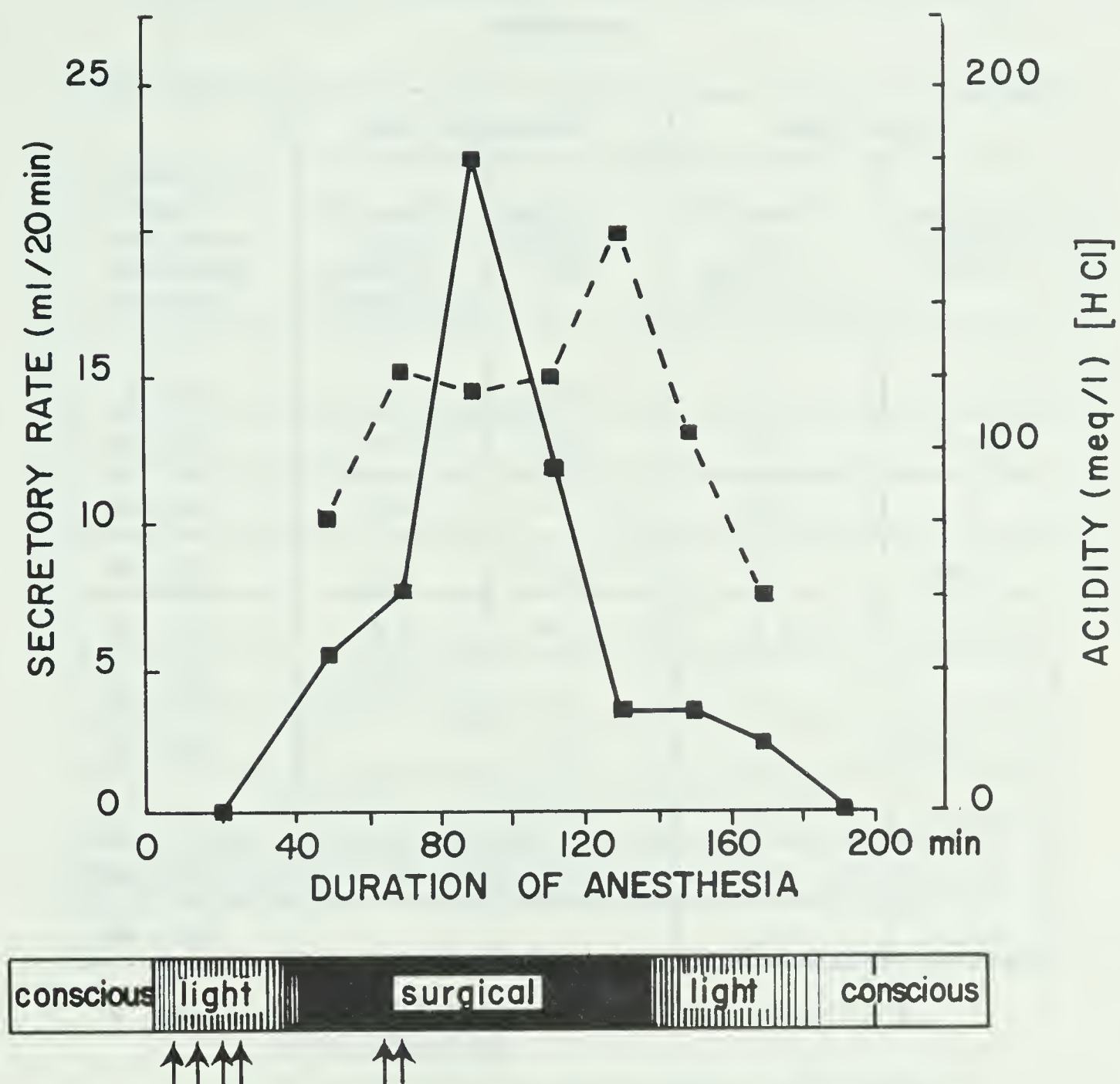


Fig. 4. Time course of gastric secretion of dog Heinz anesthetized with FBA.1420. Arrows indicate administration of supplemental doses (0.5 - 1.0 gm each) Secretory Rate, Solid Line; Acidity, Broken Line.

TABLE IV

Gastric secretory responses of dogs to chloralose-urethane*
anesthesia.

Collection Time (min after secretion started)	Dog 'Penelope'		Dog 'Louis'	
	Volume** of Gastric Juice (ml)	Acidity (meq/l of HCl)	Volume** of Gastric Juice (ml)	Acidity (meq/l of HCl)
0 - 20	1.7	65.0	0.4	37.5
20 - 40	5.3	93.0	1.0	75.0
40 - 60	5.0	--	0.5	--
60 - 80	4.1	117.0	5.0	180.0
80 - 100	2.6	84.6	4.2	107.1
100 - 120	0.0	--	--	--
120 - 140			1.2	83.3
140 - 160			1.0	30.0
160 - 180			1.0	40.0
180 - 200			1.0	30.0

* dose - 3.0 ml (1:5 chloralose-urethane solution)/kg
for dog Penelope.

2.5 ml (1:10 chloralose-urethane solution)/kg
for dog Louis.

** each sample taken represents preceding 20 minute period.

-- indicates sample not taken or analysed.

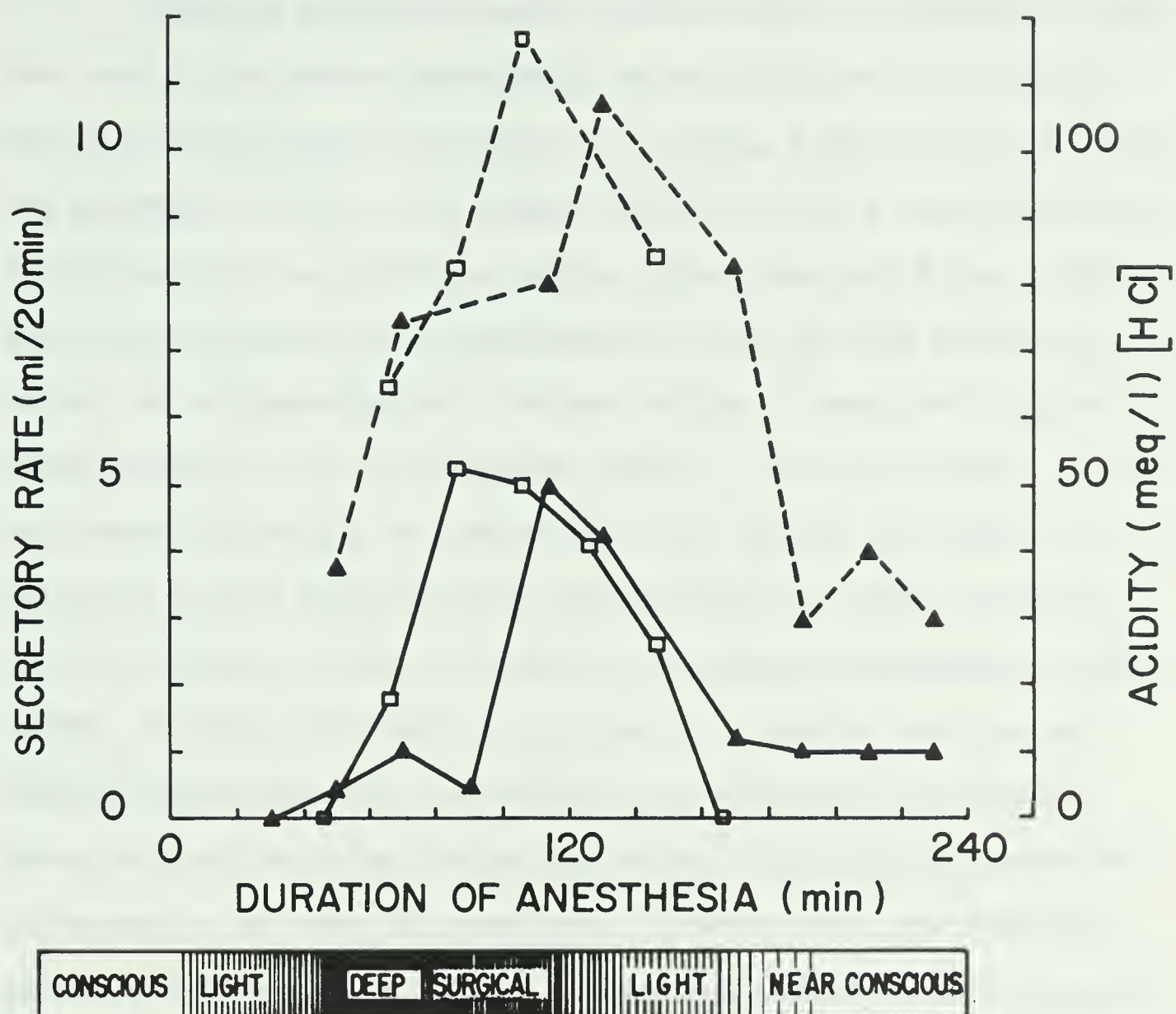


Fig. 5. Time course of gastric secretion during chloralose-urethane anesthesia. $\square$, dog Penelope anesthetized with 1:5 solution; $\blacktriangle$, dog Louis anesthetized with 1:10 solution. Secretory Rate, Solid Line; Acidity, Dotted Line.

3. Discussion.

There is excellent reason to believe that the anesthetics which were used in the present experiments differ in actions on the nervous system since each agent is capable of producing a wide variety of central and peripheral effects. For example, CI-395 is both a hallucinogen and a convulsant whereas CI-581 is neither (Chen, Ensor and Bohner, 1966). Both cyclohexylamines are sympathomimetic while FBA.1420 produces a variety of parasympathomimetic effects such as a reduction of systolic blood pressure in the dog (Doenicke, 1965). On the other hand, chloralose causes cholinergic- and adrenergic- like effects and produces a selective nervous facilitation or hyperexcitability despite sedation (Balis and Monroe, 1964). In addition to producing anesthesia, CI-395, CI-581, FBA.1420 and chloralose-urethane were found to have another pharmacological property in common viz., causing gastric secretion. Hence the question arises whether the stimulation of gastric secretion is related to the depth of anesthesia. In most cases, the observed secretory rate was maximal during surgical anesthesia while both secretory rate and acidity declined upon emergence from the general anesthetic state. A marked rise in secretion during FBA.1420 anesthesia was observed only after enough supplemental anesthetic was administered to produce surgical anesthesia. Secretion after chloralose-urethane anesthesia exhibited the longest latency. The changes in secretory rate appear to follow closely the depth of anesthesia (especially chloralose-urethane anesthesia). The finding that anesthetics with widely differing pharmacological properties can initiate gastric secretion in like manner during anesthetic states does suggest that gastric secretion might be more

closely correlated with the degree of depression of the nervous systems during anesthesia rather than to specific stimulant efficacy of the drug.

If both facilitatory and inhibitory neurones exist in the nervous mechanism controlling gastric secretion then the secretory response might be observed if either the former were excited, or if the latter inhibited. Central nervous excitation of gastric secretion by a direct action of a general anesthetic on facilitatory neurones appears unlikely for reasons already outlined by Sanders (1963). A direct release of gastrin or a direct stimulant action on the parietal cells could conceivably produce an acid secretion although this type of action by a general depressant drug has never been demonstrated. On the other hand, the secretory response to anesthesia could be explained by assuming that inhibitory neurones responsible for the control of gastric secretion are depressed by the action of an anesthetic. Inhibitory reflexes are known to exist within the walls of the stomach which inhibit the release of gastrin (Schofield, 1966). A depressant action, on intrinsic inhibitory neurones of the stomach which in the conscious state possibly act to prevent the release of gastrin or excitation of the parietal cells, therefore could cause secretion. Participation of the central nervous system in the above reflex pathways is also possible, however, since vagal afferent fibers from the stomach have been described (Murray, 1967). Moreover, since areas within the brain are known to cause secretion upon stimulation (See B-1, Introduction), a depression of inhibitory pathways involved in central autonomic control could cause gastric secretion via the vagus nerves. Understanding of the nature of the secretory response, i.e., whether it is the result of the anesthetic's

action on the central or on the peripheral nervous system, or on both, has been complicated even further by the report that although absent after vagotomy, the secretory response reappears three months post-operatively (Schachter, 1949).

C. EFFECTS OF DRUGS ON THE SECRETORY ACTIVITY OF THE STOMACH CAUSED BY GENERAL ANESTHESIA.

1. Methods

a) Control injections

The previous method of inducing chloralose-urethane anesthesia required the injection of 50 to 60 ml of the anesthetic solution. To insure that the vehicle itself played no part in the observed phenomenon, two control injections (each 50 ml of isotonic saline-Abbott, heated to 40°) were carried out in two conscious dogs, Claudia and Penelope. The intravenous administration of the vehicle to either dog did not change the neutral to alkaline reaction inside the stomach and did not cause any secretion over a period of one hour after injection.

A possibility that anesthesia-induced secretion was not restricted to general anesthetics but was a side effect of many general depressant drugs was considered. For this reason a state of quiescence and analgesia was produced in a fasted dog and the secretion of the stomach was observed. Intramuscular injections totaling 5 ml of Innovar^R-McNeil (each ml contained 0.4 mg fentanyl and 20.0 mg droperidol) produced "neuroleptanalgesia" but failed to alter the alkaline pH or initiate secretion in dog Claudia.

b) General

In the present series, secretion was induced with chloralose-urethane anesthesia and a subcutaneous injection of atropine sulfate (Glaxo-Allenburys) or intravenous injection of hexamethonium bromide (Poley) was made after the secretion was well under way.

2. Results

a) Effect of atropine on secretion induced by chloralose-urethane anesthesia

As can be seen from Fig. 6, atropine effectively antagonized the secretion evoked by chloralose-urethane anesthesia. Both volume and acidity of the secretion diminished to zero in 20 minutes in dog Curly and in 15 minutes in dog Heinz. Attempts to induce secretion after atropine by administering more anesthetic solution failed. The absence of secretion further extended into emergence from the general anesthetic state and into consciousness.

b) Effect of hexamethonium on secretion induced by chloralose-urethane anesthesia

With a dose of 2.5 mg/kg, the intravenous administration of hexamethonium produced a rapid and pronounced drop in volume and acidity of the gastric juice evoked by chloralose-urethane anesthesia. The secretion remained low for the duration of the experiment as seen from Fig. 7. 5.0 mg/kg of hexamethonium completely arrested secretion caused by chloralose-urethane anesthesia in two dogs. This effect can be seen from Fig. 8. Hexamethonium given during a high secretory rate completely abolished secretion in 15 minutes in dog Luschka and in 20 minutes in dog Heinz. Further administration of chloralose-urethane did not re-excite secretion although the pH inside the stomach remained acidic throughout the experiment and into consciousness.

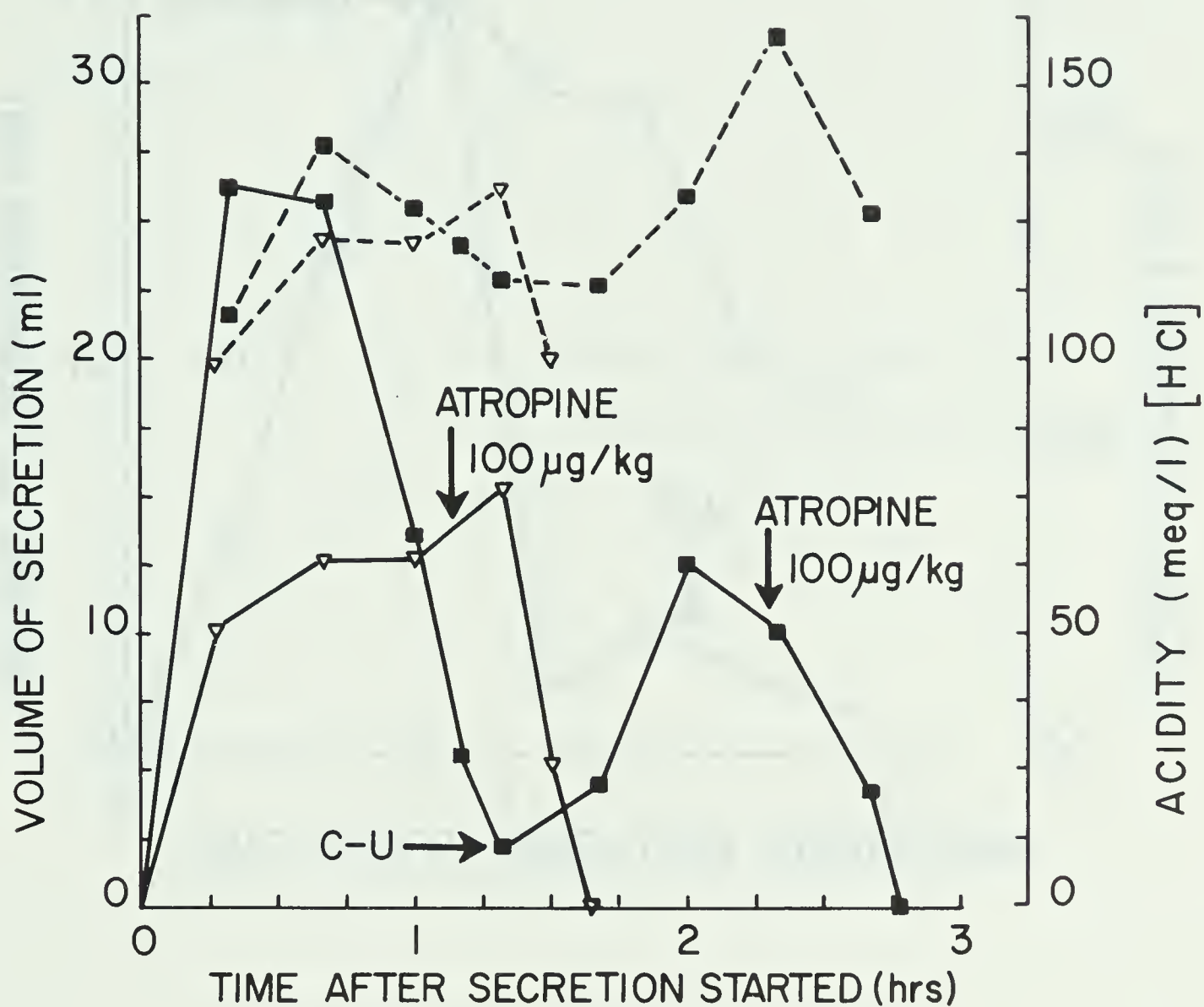


Fig. 6. Effect of atropine on volume and acidity of gastric secretion produced by chloralose-urethane anesthesia. ■, dog Heinz; ▽, dog Curly. Volume, Solid Line; Acidity, Broken Line. C-U arrow indicates administration of supplemental dose of chloralose-urethane.

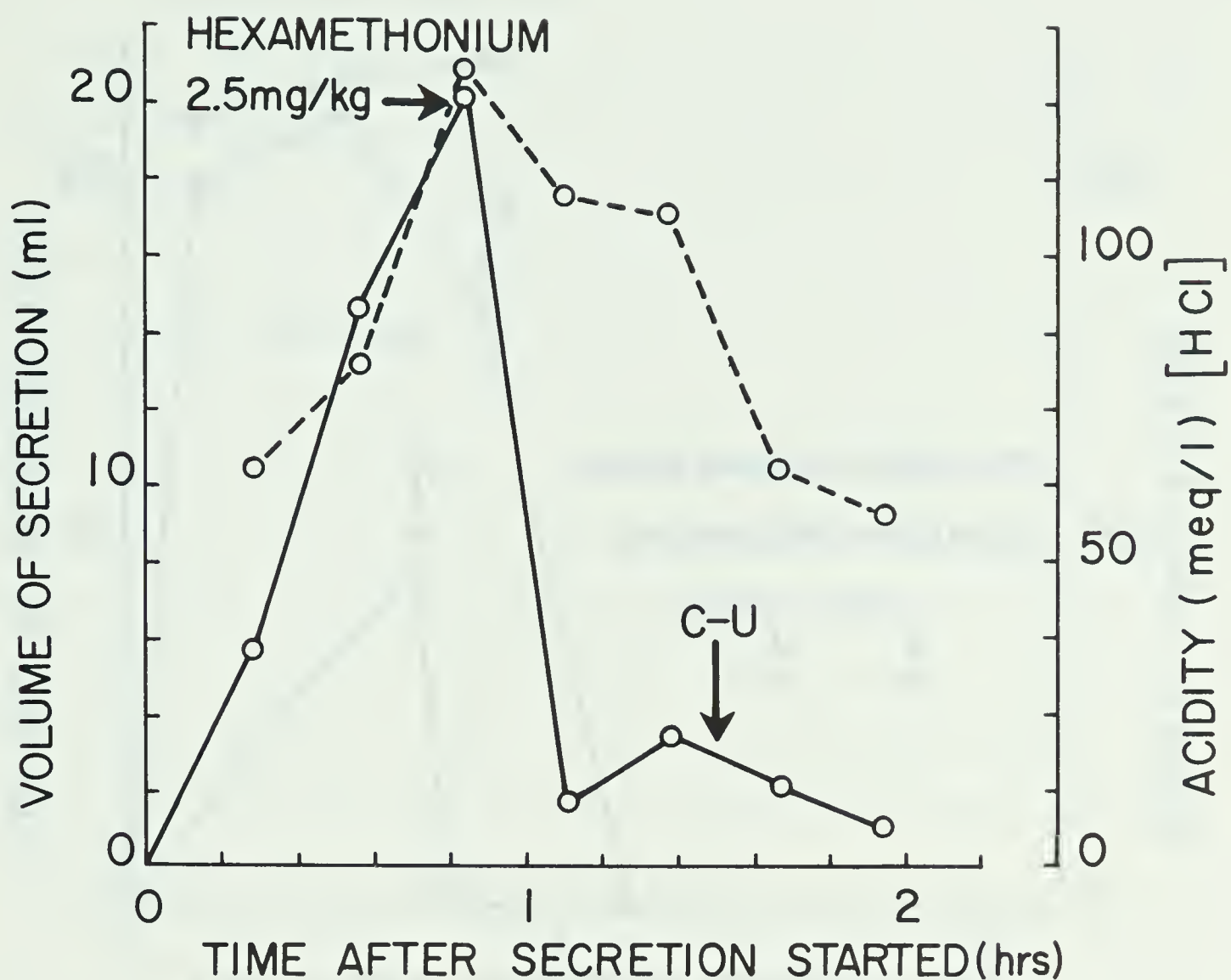


Fig. 7. Effect of hexamethonium on volume and acidity of gastric secretion produced by chloralose-urethane anesthesia in dog Claudia. Volume, Solid Line; Broken Line, C-U arrow indicates administration of supplemental dose of chloralose-urethane.

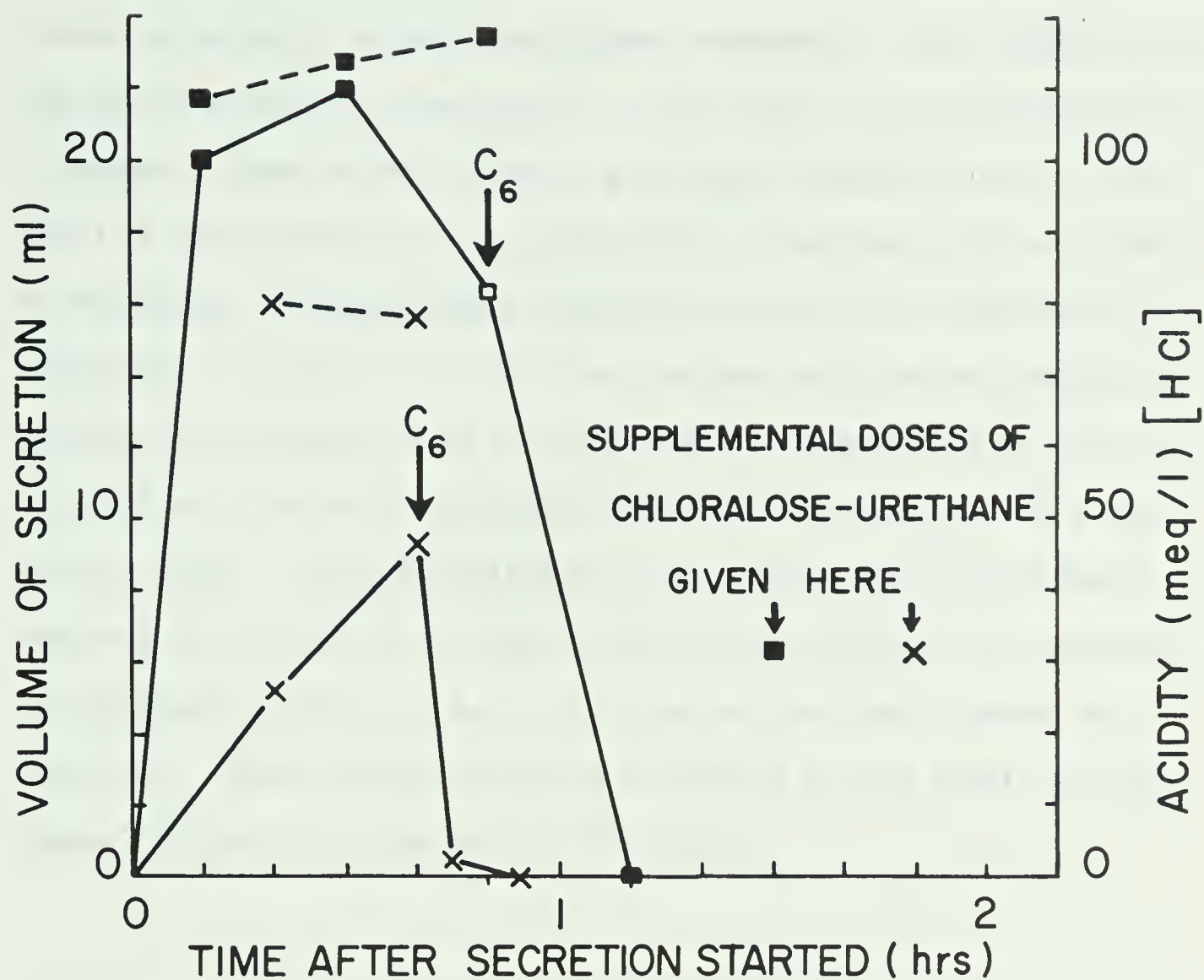


Fig. 8. Effect of hexamethonium (5.0 mg/kg) on volume and acidity of gastric secretion produced by chloralose-urethane anesthesia. $\blacksquare$, dog Heinz; x, dog Luschka. Volume, Solid Line; Acidity, Broken Line. C_6 arrows indicate administration of hexamethonium.

3. Discussion

In the present experiments, atropine was demonstrated to abolish secretion evoked by chloralose-urethane anesthesia. This suggests that the effect produced by anesthesia is cholinergic or parasympathomimetic in nature. Since hexamethonium, a ganglionic blocking drug, was also found in the present series to effectively antagonize secretion evoked by anesthesia, a preganglionic excitatory action by the anesthetic is indicated. In this view, chloralose-urethane would not be causing the release of acetylcholine by a direct action on a postganglionic nerve cell but by a central or preganglionic action which results in a vagomimetic effect. The possibility that chloralose-urethane anesthesia prevents the release of an inhibitory substance either at the ganglia or postganglionically, or has a nicotinic action itself, cannot be ruled out. These possibilities are considered in more detail in the General Discussion at the end of this thesis.

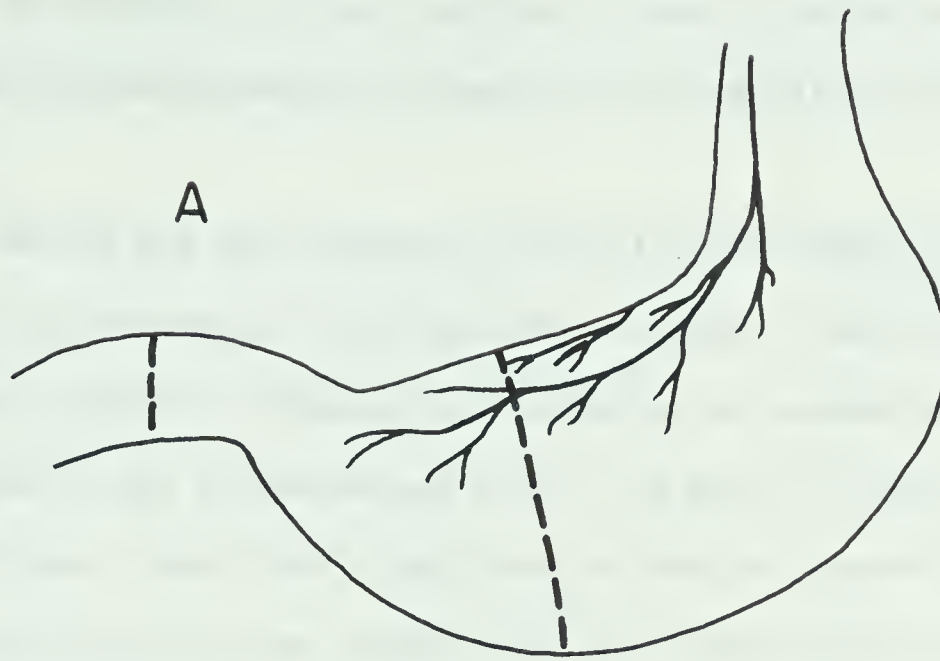
D. EFFECTS OF CHLORALOSE-URETHANE ANESTHESIA ON SECRETION OF THE STOMACH AFTER PYLORIC ANTRECTOMY.

1. Surgical preparation

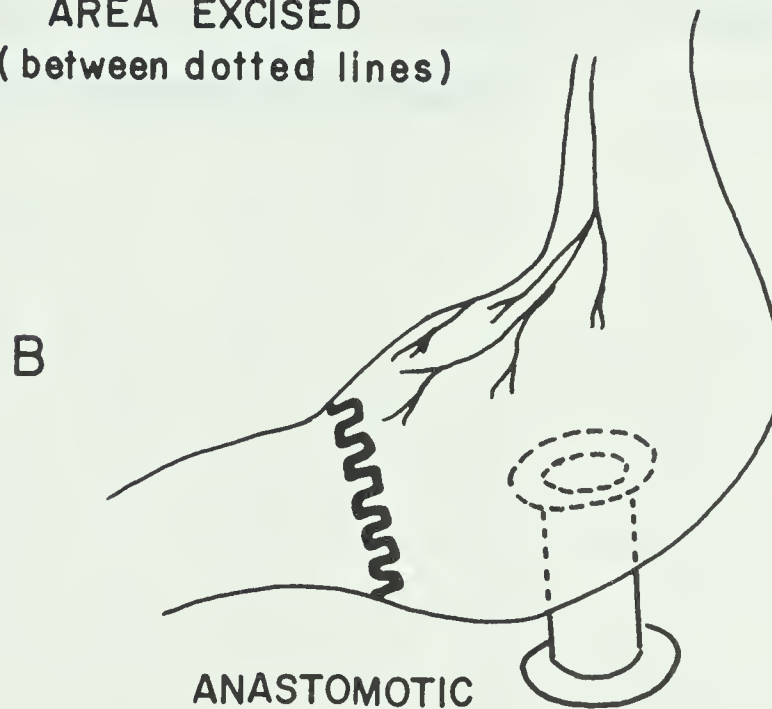
Following induction of anesthesia with intravenous sodium pentobarbital (35 mg/kg), the dog (Peter) was placed in the supine position, the abdomen shaved and cleansed with disinfectant.

All surgery was carried out using sterile technique. After a 20 cm midline laparotomy, the stomach and duodenum were delivered into the wound and freeing of the lesser and greater curvatures of the vascular omentum was begun using ligation and division in continuity. Both antrum and pylorus were removed intact between crushing clamps. The gastro-duodenostomy was performed using continuous 3-0 silk through all free edge tissue layers. Several interrupted 3-0 silk seromuscular layer sutures were placed on the anterior border of the anastomosis. The cannula was installed and the abdomen closed by the surgical technique described earlier and the animal was allowed six weeks to recover.

Fig. 9 illustrates the position of the cannula and the amount of resection of the stomach. Post-mortem histological examination of several hemotoxylin-eosin stained sections near the anastomotic site revealed an abundance of pink-colored parietal cells characteristic of the fundal stomach.



AREA EXCISED
(between dotted lines)



ANASTOMOTIC
SITE

Fig. 9. (A) Diagram of the stomach showing the area of excision in pyloric antrectomy operation.

(B) Diagram of the stomach showing positioning of cannula in resected portion of fundic stomach.

2. Results

The purpose of this study was to see if chloralose-urethane anesthesia produces gastric secretion in a dog with the pyloric antrum removed.

During the pre-induction period in both experiments, the secretion of a bile-stained fluid (pH 7-8) occurred. The results of the secretion collected following the induction of chloralose-urethane anesthesia in the antrectomized animal are given in Table V. It should be noted that a small but significant secretion occurred early in one experiment while only an acidic pH on the stomach walls was observed in the other. The observations were carried out in experiment 1 for the full duration of anesthesia (2.5 hours).

TABLE V

Secretion collected from pyloric antrectomized stomach of dog
'Peter' anesthetized with 1:10 chloralose-urethane

Collection Time (min after secretion started)	Experiment #1		Experiment #2	
	Volume* of Collection (ml)	Remarks**	Volume* of Collection (ml)	Remarks**
0 - 20	1.4	35 meq/l (HCl)	10.0	Bile
20 - 30	--	--	0.0	pH 3-4
30 - 40	1.5	33 meq/l (HCl)	1.6	Bile pH 1-2
40 - 50	--	--	7.0	Bile pH 5-6
50 - 60	11.7	Bile	11.2	Bile pH 6
60 - 70	--	--	8.7	Bile pH 6-7
70 - 80	11.2	Bile	2.8	Bile pH neutral
80 - 90	--	--	5.4	Bile
90 - 100	6.3	Bile	0.3	Bile

* each sample taken represents amount taken in preceding 10 or 20 minute period.

** Bile indicates substance collected which was pH 7-8.
pH values listed refer to pH reaction inside stomach on walls.

-- indicates sample not taken.

3. Discussion

The results on the antrectomized animal must be interpreted with caution. The reflux of bile from the duodenum can be cited as a reason for the high pH of the secretion. Thus, the definite although small amount of gastric acid secretion observed early in one experiment and the highly acidic reaction in the stomach in the other, suggest that the secretion caused by chloralose-urethane anesthesia is not completely abolished by pyloric antrectomy. Since removal of the pyloric antrum should have removed the source of gastrin, these data indicate that chloralose-urethane anesthesia may cause gastric secretion in the dog with an intact stomach by effecting a release of gastrin. The implication of cholinergic stimuli in this phenomenon was discussed in the earlier section and hence the inference may be drawn that both acetylcholine and gastrin are released during chloralose-urethane anesthesia and both subsequently act either singly or in concert to produce acid secretion. The experimental conditions of this study i.e., the refluxing of contents from the duodenum and the contamination of the samples of gastric secretion with bile prevent definite conclusions. The results are, however, suggestive that the pyloric antrum plays some role in the secretion produced during anesthesia. Further experiments are desirable to clarify this matter.

E. EFFECTS OF VOLATILE ANESTHETICS ON GASTRIC SECRETION.

1. General method

Induction of anesthesia was achieved by administering 5% halothane by mask. The halothane (Ayerst) was vaporized with oxygen in a Verni-trol^R-Ohio and administered through a closed circuit Heidbrink anesthetic machine equipped with a CO₂ absorber. The animal was then intubated and allowed to breathe oxygen before being 'titrated' to the desired anesthetic depth with 0.75% halothane.

When the effects of 1% methoxyflurane were studied, the animal was first anesthetized by mask with 5% halothane produced in a Fluotec^R vaporizer. Methoxyflurane (Abbott), vaporized in the Verni-trol with 95% oxygen-5% carbon dioxide mixture, was then administered endotracheally to maintain anesthesia.

The final experiments were carried out with a 3.5% methoxyflurane emulsion prepared by the method of Krantz, Cascorbi, Helrich, Burgison, Gold and Rudo (1961) and given intravenously. A Rochester needle was used to cannulate the cephalic vein for the purpose of multiple injections. The injections required the use of large volumes (10 to 25 ml) but large volumes of intravenously injected vehicle failed to alter the alkaline pH in the stomach of a dog (Hamlet) over an observed period of twenty minutes.

2. Results

a) Responses to induction and maintenance of anesthesia with halothane

The endotracheal administration of halothane in concentrations of 0.75 to 5% (volume/volume) did not cause gastric secretion through a full range of anesthetic depths. Little excitement occurred in dog Penelope during the induction process and minimal restraint was used. The pH inside the stomach remained near neutrality. Similar observations were made on dog Claudia anesthetized with halothane although the pH inside the stomach changed briefly to about 3-4 during light anesthesia.

b) Responses to methoxyflurane anesthesia induced by halothane

Maintenance of anesthesia with endotracheal or mask administered methoxyflurane failed to produce any detectable secretion but changed the pH inside the stomach of dog Monroe and dog Penelope to a low value (pH 2-3) during light anesthesia. The animals were observed in the anesthetized state from surgical depth to consciousness.

c) Responses to intravenously administered methoxyflurane

The intravenous administration of a 3.5% methoxyflurane emulsion produced gastric secretion of low acidity in two dogs. The results are summarized in Table VI. The latency of onset of secretion was very short (about 3 minutes) in either dog. Anesthesia was not taken beyond surgical depth and neither dog secreted after emergence from the general anesthetic state.

TABLE VI

Gastric secretory responses of dogs to intravenously
administered methoxyflurane*

Collection Time (min after secretion started)	Dog 'Curly'		Dog 'Penelope'	
	Volume** of Gastric Juice (ml)	Acidity (meq/l of HCl)	Volume** of Gastric Juice (ml)	Acidity (meq/l of HCl)
0 - 20	8.0	43.7	5.0	70.0
20 - 40	0.0	--	5.5	69.1
40 - 60	--	--	6.1	68.8

* dose - 3.0 ml/kg of 3.5% emulsion and supplemented thereafter according to requirements of the animal.

** each sample represents preceding 20 minute period.

-- indicates sample not taken.

3. Discussion

The existence of "opposing" actions of general inhalation anesthetics on nervous control of gastric secretion is possible. Halothane inhibits the activity of ganglia of the gastrointestinal tract and leaves intact the effects of the administration of drugs with direct action on glands and muscle (Raventos, 1961). Thus if the ganglia within the walls of the stomach equilibrate with halothane or methoxyflurane before significant saturation of the central nervous mechanism controlling acid secretion has occurred, gastric secretion would not be expected to be produced because of a peripheral ganglionic block. In addition, anesthetics given by the inhalation route might represent a noxious form of stimulus e.g., the intubation process and the irritating odor, which may inhibit secretion, since Schachter (1949) has demonstrated that nociceptive stimuli inhibit acid secretion caused by anesthesia. During very light methoxyflurane anesthesia, however, a pH change to high acidity was observed suggesting a differential response which is dose dependent. Thus the stimulant effect of intravenously administered methoxyflurane might also be observed with inhaled methoxyflurane if equipotent doses were used or the same tissue distribution of the anesthetic occurred. The possible interference of halothane induction exerting an inhibitory effect on the autonomic ganglia during methoxyflurane anesthesia also cannot be ruled out although halothane should have reached negligible concentrations in a very short time. The stimulant effect of methoxyflurane given intravenously is like that of other intravenous anesthetics and suggests that no general pattern of chemical structure is associated with the anesthetic's efficacy to produce the secretory response.

III. GENERAL DISCUSSION

GENERAL DISCUSSION

The observations of this investigation have already been discussed briefly in various sections of this thesis. It therefore remains to summarize succinctly the most pertinent points for discussion. These are presented below.

The results of experiments carried out over nearly a century (see B-1, Introduction) indicate that a localized group of neurones, specifically responsible for the central control of gastric secretory activity, do not exist. Most of the central neurones which on stimulation have been found to excite secretion lie within the limbic system and hypothalamus and descend by an unknown route to the vagal nuclei. Electrical stimulation of neurones which depress gastric secretion has not been thoroughly investigated, and the existence of inhibitory fibers suppressing the excitatory fibers controlling gastric secretion is largely inferential. On the other hand, it is commonly recognized that light anesthesia may be attended by various manifestations indicating a release of lower parts of the nervous system, including the autonomic nervous system, from cortical inhibitory influences (French et al., 1953b). Balis and Monroe (1964) have suggested that motor hyperexcitability evoked by alpha-chloralose can be explained as "a result of a temporally and spatially differential depressant action which disrupts the negative feedback of the reticulo-cortico-reticular loop". If such disruption was brought about by the depressant action of general anesthetics, and if a group of neurones in reticular structures which act specifically to control gastric secretion exist (see B-1, Introduction),

then an elimination of descending inhibitory influences on the hypothalamus and mesencephalic reticular formation could cause gastric secretion. Thus, one possibility is that anesthesia causes gastric secretion by disinhibiting inhibitory neurones in the central autonomic control of gastric secretion.

Another possibility, however, is that peripheral nervous mechanisms are involved in the gastric secretory response during anesthesia. For example, as already discussed (Page 39), inhibitory reflexes are known to exist which inhibit the release of gastrin (Schofield, 1966). The results presented here, though not certain, suggest that gastrin is to some extent involved in the secretory phenomenon. Inhibition by anesthetics of such a peripheral inhibitory reflex could facilitate secretion. Further, there is good evidence (Paton and Vizi, 1969) that autonomic postganglionic cholinergic neurones may be under a tonic presynaptic inhibition by sympathetic adrenergic neurones. Paton and Vizi conclude from their studies on intestinal muscle strips "that for a tissue under dual autonomic control, withdrawal of sympathetic control will lead to a parasympathetic response which is not only unopposed but also itself enhanced". If anesthesia were to selectively or preferentially inhibit such assumed sympathetic neurones to the gastric secretory mechanism an elegant explanation for the response to anesthesia would exist.

It is clear that the experiments of this investigation do not provide a final and satisfactory explanation for anesthesia-initiated secretion. They do, however, establish clearly that anesthetics, in general, produce gastric secretion in the dog under certain circumstances.

The fact remains that an analysis of the mechanism involved will not be easy since surgical trauma which may be required for physiological analysis (denervations, etc.) inhibits the effect. It would seem, therefore, that a successful interpretation will have to be more indirect, possibly by the use of future drugs with highly selective actions.

IV. SUMMARY AND CONCLUSIONS

SUMMARY AND CONCLUSIONS

1. The general anesthetics, CI-395, CI-581, FBA.1420, and chloralose-urethane produced gastric secretion of high acidity in the gastrostomized stomach of dogs which exhibited no basal secretion or acidity prior to the induction of anesthesia with these agents. The secretion appeared to be correlated with the depth of anesthesia.
2. Atropine or hexamethonium administered to gastrostomized dogs anesthetized with chloralose-urethane completely antagonized the gastric secretion evoked by the anesthetic. This suggests that the secretory response is of a cholinergic nature and the action whereby anesthesia produces the secretion is of preganglionic origin.
3. The gastric secretion evoked by chloralose-urethane anesthesia was much reduced though not abolished after removal of the pyloric antrum in one dog. This observation suggests that gastrin participates in the secretory response to anesthesia in the dog.
4. The volatile anesthetics, halothane and methoxyflurane did not cause gastric secretion when given to gastrostomized dogs in doses producing light, surgical, or deep anesthesia. Methoxyflurane, however, given intravenously, did cause a small but measureable secretion.
5. The possible mechanisms involved in the observed gastric secretion are discussed. A new possibility has been presented, viz., that the secretion which results during anesthesia is due to either an inhibition of a central inhibitory control mechanism or an inhibition of similar peripheral autonomic nerves.

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